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(73) Proprietor: **Southern Research Institute
Birmingham Alabama 35205 (US)**

(72) Inventors:
• **TICE, Thomas, R.
Birmingham, AL 35244 (US)**
• **GILLEY, Richard, M.
Birmingham, AL 35120 (US)**

(74) Representative: **Leissler-Gerstl, Gabriele
Eisenführ, Spelser & Partner,
Patentanwälte,
Arnulfstrasse 25
80335 München (DE)**

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Description**TECHNICAL FIELD**

5 **[0001]** The present invention relates to a method of microencapsulating an agent to form a microencapsulated product and in particular to a method to prepare microcapsules, microspheres, nanocapsules and nanospheres. More particularly, the present invention relates to an emulsion-based method for preparing capsules or microspheres containing water-soluble or oil-soluble agents, particularly highly water-soluble agents.

BACKGROUND ART

10 **[0002]** Microcapsules and microspheres are usually powders consisting of spherical particles 2 millimeters or less in diameter, usually 50 microns or less in diameter. If the particles are less than 1 micron, they are often referred to as nanocapsules or nanospheres. For the most part, the difference between microcapsules and nanocapsules is their size; their internal structure is about the same. Similarly, the difference between microspheres and nanospheres is their size; their internal structure is about the same.

15 **[0003]** A microcapsule (or nanocapsule) has its encapsulated material, herein after referred to as agent, centrally located within a unique membrane, usually a polymeric membrane. This membrane may be termed a wall-forming material and is usually a polymeric material. Because of their internal structure, permeable microcapsules designed for controlled-release applications release their agent at a constant rate (zero-order rate of release). Also, impermeable microcapsules can be used for rupture-release applications. Hereinafter, the term microcapsules will include nanocapsules, microbubbles (hollow particles), porous microbubbles and particles in general that comprise a central core surrounded by a unique outer membrane.

20 **[0004]** A microsphere has its agent dispersed throughout the particle; that is, the internal structure is a matrix of the agent and excipient, usually a polymeric excipient. Usually controlled-release microspheres release their agent at a declining rate (first order). But microspheres can be designed to release agents at a near zero-order rate. Microspheres tend to be more difficult to rupture as compared to microcapsules because their internal structure is stronger. Hereinafter, the term microsphere will include nanospheres, microparticles, nanoparticles, microsponges (porous microspheres) and particles in general, with an internal structure comprising a matrix of agent and excipient.

25 **[0005]** A wide variety of methods to prepare microcapsules and microspheres are described in the literature. Several of these methods make use of emulsions to make microspheres, in particular, to make microspheres less than 2 millimeters in diameter. To give a general example of such processes, one can dissolve a polymer in a suitable organic solvent (the polymer solvent), dissolve or disperse an agent in this polymer solution, disperse the resulting polymer/agent mixture into an aqueous phase (the process medium) to obtain an oil-in-water emulsion with oil microdroplets dispersed in the processing medium, and remove the solvent from the microdroplets to form microspheres. These processes can also be performed with water-in-oil emulsions and with double emulsions.

30 **[0006]** The use of emulsion-based processes that follow this basic approach is described in several U.S. patents. For example, U.S. Patent No. 4,384,975 describes the production of microspheres by forming an emulsion and then slowly removing the polymer solvent from the microdroplets in the emulsion by vacuum distillation. As another example, U.S. Patent No. 3,891,570 discloses a method in which the polymer solvent is removed from the microdroplets in the emulsion by applying heat or reducing the pressure in the fabrication vessel. In still another example, U.S. Patent No. 4,389,330, the polymer solvent is partially removed from the microdroplets in the emulsion by vacuum distillation (preferably 40 to 60% of the polymer solvent) and then the remainder of the polymer solvent is extracted to solidify the microspheres.

35 **[0007]** The disadvantage of the above-described processes, as with other emulsion-based processes, is that certain agents can partition into the processing medium, that is, the agents migrate out of the microdroplets during the polymer solvent removal step, resulting in a poor encapsulation efficiency. Furthermore, all of the above-described processes afford microspheres rather than microcapsules.

40 **[0008]** Another emulsion-based method to prepare microspheres described in U.S. Patent No. 3,737,337 uses a controlled extraction of the polymer solvent from the microdroplets by adding processing medium to the emulsion at a controlled rate. However, this patent teaches away from the present invention by disclosing that the extraction must proceed slowly or no spherical particles will be formed. Similarly, U.S. Patent No. 4,652,441 describes a method to encapsulate water-soluble agents from water-in-oil-in-water emulsions, and teaches that a high-viscosity, drug-retaining substance must be included in the inner water phase to retain the drug in the microdroplets during evaporation of the polymer solvent. U.S. Patent No. 4,652,441 also teaches against the present invention by suggesting that it is impossible to effectively encapsulate water-soluble agents without using drug-retaining substances in the emulsion.

45 **[0009]** US-A-3943063 discloses a process for preparing microcapsules in which (1) a core substance is dispersed or dissolved in a film-forming polymer; (2) this dispersion or solution is emulsified in a vehicle (or continuous process

medium) which is poorly miscible with the solvent of the polymer solution, does not dissolve the polymer and does not dissolve the core substance; and (3) to this emulsion is added a non-solvent for the polymer (extraction medium) that is miscible with the solvent, poorly miscible with the vehicle, and does not dissolve the polymer.

[0010] DE-A-2930248 discloses a process which is similar to that of US-A-3943063.

[0011] It was known from EP - 0266119 to prepare water-soluble antigen-loaded microcapsules by emulsifying a mixture (the mixture contained a wall-forming polymer dissolved in a solvent and an antigen dissolved in water) in an aqueous process medium; stirring the resultant emulsion for 10 minutes and transferring it to deionized water for extraction. This method gives an encapsulation efficiency of 7,5 %.

SUMMARY OF THE INVENTION

[0012] Accordingly, one object of the present invention is to provide an emulsion-based method for preparing microspheres with agents that have a high propensity to partition within minutes into the processing medium, the continuous phase of the emulsion. Another object of the present invention is a method to prepare microcapsules, as well as microspheres, from an emulsion. Yet another object of the invention is to provide a method for preparing microspheres or microcapsules containing an agent that has a solubility of greater than 10 milligrams per millileter in the processing medium. Yet another object of the invention is to control the porosity of the wall of the microcapsules or the excipient of microspheres by controlling the rate of extraction of the solvent from the microdroplets of the emulsion. Yet another object of the present invention is to provide a method for making microcapsules and microspheres having diameters from less than 1 micron to greater than 2 millimeters. Still another object of the present invention is to provide a method for preparing drug-loaded microspheres and microcapsules that result in free-flowing powders of unagglomerated spherical particles suitable for parenteral as well as other routes of drug administration.

[0013] According to the invention there is provided a method of microencapsulating an agent, to form a microencapsulated product, comprising:

- a) dispersing an effective amount of the agent in a solvent containing a dissolved wall forming material to form a dispersion;
- b) combining the dispersion with an effective amount of a continuous process medium to form an emulsion that contains the process medium and microdroplets comprising the agent, the solvent and the wall-forming material within 30 seconds; and
- c) immediately within up to three minutes after the formation of the emulsion adding all at once the emulsion to an effective amount of an extraction medium to extract the solvent from the microdroplets to form the microencapsulated product, wherein the solvent has a solubility in the extraction medium from about 1 part per 100 to about 25 parts per 100.

[0014] Preferably, this invention involves (1) dissolving or otherwise dispersing one or more agents (liquids or solids) in a solvent containing one or more dissolved wall-forming material or excipients (usually the wall-forming material or excipient is a polymer dissolved in a polymer solvent); (2) dispersing the agent/polymer-solvent mixture (the discontinuous phase) into a processing medium (the continuous phase which is preferably saturated with polymer solvent) to form an emulsion; and (3) transferring all of the emulsion immediately to a large volume of processing medium or other suitable extraction medium to immediately extract the solvent from the microdroplets in the emulsion to form a microencapsulated product, such as microcapsules or microspheres. The particular features of this technique that distinguish its uniqueness are described below.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] One of the important features of this microencapsulation technique is the rate of polymer solvent removal from the microdroplets of the emulsion. By adding the emulsion to the processing medium all at once and thereby removing most of the polymer solvent very rapidly (within 3 minutes), agents highly soluble in the processing medium can be encapsulated as well as less soluble agents.

[0016] The existing literature on the microencapsulation of water-soluble agents teaches that water-soluble agents, especially if high loadings such as greater than 10 wt% and particularly greater than 30 wt % are desired, cannot be easily encapsulated by oil-in-water emulsion-based processes because of the tendency of the agent to migrate out of the organic microdroplets into the aqueous processing medium. This agent migration is greater with small emulsion microdroplets because of their increased surface area. The advantage of this invention over other emulsion-based processes is that highly water-soluble agents, such as agents with water solubilities as high as 2 grams per milliliter, can be effectively encapsulated at loadings of up to 80 wt %. Moreover, the resultant microspheres or microcapsules are free-flowing powders of spherical particles. Depending on the processing conditions, these particles can have

diameters ranging from less than 1 micron to greater than 2 millimeters.

[0017] To prepare microcapsules or microspheres by this invention, a suitable wall-forming material, such as a polymer, is first dissolved or otherwise dispersed in a solvent. The term wall-forming material also denotes unique membranes and excipients. The solvent used to dissolve the wall material or excipient can be selected from a variety of common organic solvents including halogenated aliphatic hydrocarbons such as methylene chloride, chloroform, and the like; alcohols; aromatic hydrocarbons such as toluene and the like; halogenated aromatic hydrocarbons; ethers such as methyl t-butyl ether and the like; cyclic ethers such as tetrahydrofuran and the like; ethyl acetate; diethyl carbonate; acetone; cyclohexane; and water. These solvents may be used alone or in combination. The solvent chosen must be a material that will dissolve the wall material or excipient and it is best that it is chemically inert with respect to the agent being encapsulated and the polymer. Moreover, the solvent must have limited solubility in the extraction medium. Generally, limited solubility means having a solubility from about 1 part per 100 to about 25 parts per 100.

[0018] Suitable wall-forming materials include, but are not limited to: poly(dienes) such as poly(butadiene) and the like; poly(alkenes) such as polyethylene, polypropylene, and the like; poly(acrylics) such as poly(acrylic acid) and the like; poly(methacrylics) such as poly(methyl methacrylate), poly(hydroxyethyl methacrylate), and the like; poly(vinyl ethers); poly(vinyl alcohols); poly(vinyl ketones); poly(vinyl halides) such as poly(vinyl chloride) and the like; poly(vinyl nitriles); poly(vinyl esters) such as poly(vinyl acetate) and the like; poly(vinyl pyridines) such as poly(2-vinyl pyridine), poly(5-methyl-2-vinyl pyridine) and the like; poly(styrenes); poly(carbonates); poly(esters); poly(orthoesters); poly(esteramides); poly(anhydrides); poly(urethanes); poly(amides); cellulose ethers such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, and the like; cellulose esters such as cellulose acetate, cellulose acetate phthalate, cellulose acetate butyrate, and the like; poly(saccharides), proteins, gelatin, starch, gums, resins, and the like. These materials may be used alone, as physical mixtures (blends), or as copolymers. A preferred group of wall-forming materials include biodegradable polymers such as poly(lactide), poly(glycolide), poly(caprolactone), poly(hydroxybutyrate), and copolymers thereof, including but not limited to poly(lactide-co-glycolide), Poly(lactide-co-caprolactone) and the like.

[0019] The liquid or solid agent to be encapsulated is then dispersed or dissolved in the solvent containing the dissolved wall-forming material or excipient. Examples of biological agents that may be encapsulated by this technique include, but are not limited to: analgesics such as acetaminophen, acetylsalicylic acid, and the like; anesthetics such as lidocaine, xylocaine, and the like; anorexics such as dexedrine, phendimetrazine tartrate, and the like; antiarthritics such as methylprednisolone, ibuprofen, and the like; antiasthmatics such as terbutaline sulfate, theophylline, ephedrine, and the like; antibiotics such as sulfisoxazole, penicillin G, ampicillin, cephalosporins, amikacin, gentamicin, tetracyclines, chloramphenicol, erythromycin, clindamycin, isoniazid, rifampin, and the like; antifungals such as amphotericin B, nystatin, ketoconazole, and the like; antivirals such as acyclovir, amantadine, and the like; anticancer agents such as cyclophosphamide, methotrexate, etretinate, and the like; anticoagulants such as heparin, warfarin, and the like; anticonvulsants such as phenytoin sodium, diazepam, and the like; antidepressants such as isocarboxazid, amoxapine, and the like; antihistamines such as diphenhydramine HCl, chlorpheniramine maleate, and the like; hormones such as insulin, progestins, estrogens, corticoids, glucocorticoids, androgens, and the like; tranquilizers such as thiorazine, diazepam, chlorpromazine HCl, reserpine, chlordiazepoxide HCl, and the like; antispasmodics such as belladonna alkaloids, dicyclomine hydrochloride, and the like; vitamins and minerals such as essential amino acids, calcium, iron, potassium, zinc, vitamin B₁₂, and the like; cardiovascular agents such as prazosin HCl, nitroglycerin, propranolol HCl, hydralazine HCl, verapamil HCl, and the like; enzymes such as lactase, pancrelipase, succinic acid dehydrogenase, and the like; peptides and proteins such as LHRH, somatostatin, calcitonin, growth hormone, growth releasing factor, angiotensin, FSH, EGF, vasopressin, ACTH, human serum albumin, gamma globulin, and the like; prostaglandins; nucleic acids; carbohydrates; fats; narcotics such as morphine, codeine, and the like; psychotherapeutics; antimalarials; L-dopa; diuretics such as furosemide, spironolactone, and the like; antiulcer drugs such as ranitidine HCl, cimetidine HCl, and the like.

[0020] Immunological agents that can be encapsulated by this method include: interleukins, interferon, colony stimulating factor, tumor necrosis factor, and the like; allergens such as cat dander, birch pollen, house dust mite, grass pollen, and the like; antigens of such bacterial organisms as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Corynebacterium diphtheriae*, *Listeria monocytogenes*, *Bacillus anthracis*, *Clostridium tetani*, *Clostridium botulinum*, *Clostridium perfringens*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Streptococcus mutans*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Haemophilus parainfluenzae*, *Bordetella pertussis*, *Francisella tularensis*, *Yersinia pestis*, *Vibrio cholerae*, *Legionella pneumophila*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Treponema pallidum*, *Leptospira interrogans*, *Borrelia burgdorferi*, *Campylobacter jejuni*, and the like; antigens of such viruses as smallpox, influenza A and B, respiratory syncytial, parainfluenza, measles, HIV, varicella-zoster, herpes simplex 1 and 2, cytomegalovirus, Epstein-Barr, rotavirus, rhinovirus, adenovirus, papillomavirus, poliovirus, mumps, rabies, rubella, coxsackieviruses, equine encephalitis, Japanese encephalitis, yellow fever, Rift Valley fever, lymphocytic choriomeningitis, hepatitis B, and the like; antigens of such fungal, protozoan, and parasitic organisms such as *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Candida albicans*, *Candida tropicalis*, *Nocar-*

dia asteroides, Rickettsia rickettsii, Rickettsia typhi, Mycoplasma pneumoniae, Chlamydia psittaci, Chlamydia trachomatis, Plasmodium falciparum, Trypanosoma brucei, Entamoeba histolytica, Toxoplasma gondii, Trichomonas vaginalis, Schistosoma mansoni, and the like. These antigens may be in the form of whole killed organisms, peptides, proteins, glycoproteins, carbohydrates, or combinations thereof.

[0021] Examples of non-biological agents that can be encapsulated by this method include, but are not limited to, adhesives, pesticides, fragrances, antifoulants, dyes, salts, oils, inks, cosmetics, catalysts, detergents, curing agents, flavors, foods, fuels, herbicides, metals, paints, photographic agents, biocides, pigments, plasticizers, propellents, solvents, stabilizers, polymer additives and the like.

[0022] After the agent is added to the wall-material/excipient solvent, the agent and wall-material/excipient solvent mixture dispersion is added to a continuous process medium to form microdroplets. This process medium is generally water, although organic solvents and oils can also be used when water is used to dissolve the wall material or excipient. The process medium preferably contains surfactants to allow the formation of a stable emulsion and prevent agglomeration. Examples of cationic, anionic, and nonionic compounds that can be used as surfactants include, but are not limited to, poly(vinyl alcohol), carboxymethyl cellulose, gelatin, poly(vinyl pyrrolidone), Tween 80, Tween 20, and the like. The concentration of surfactant in the process medium should be sufficient to stabilize the emulsion. The concentration of surfactant present will affect the final size of the microcapsules or microspheres. Generally the concentration of the surfactant in the process medium will be wall material/excipient from 0.1% to about 20% depending on the surfactant, the polymer solvent, and the processing medium used.

[0023] Prior to the addition of the mixture containing the dissolved wall material/excipient, its solvent and the agent, the process medium is saturated with the same solvent used to dissolve the wall material/excipient to prevent any extraction of solvent from the microdroplets during formation of the emulsion. The process medium is then mechanically agitated with devices such as homogenizers, propellers, or the like as the agent/wall material/solvent mixture is added to the process medium. During this step of the process, no solvent is evaporated or removed from the microdroplets. The temperature at which the emulsion is formed is not particularly critical, except that it must be within a range that will prevent the solvent from boiling or the process medium from gelling or freezing or the agent or wall material from degrading. The time required to form an emulsion is quite short. Generally, emulsions can be formed within 30 seconds to 5 minutes, depending upon the surfactant used and the method of agitation of the process medium.

[0024] As soon as an emulsion forms, all of the process medium containing the organic microdroplets is transferred, as quickly as possible, to an extraction medium so that greater than 20% to 30% of the solvent is immediately removed from the microdroplets (i.e., within 3 minutes). Normally, water is used as the extraction medium but other solvents or oils can also be used. In addition, salts may be added to the extraction medium to adjust its ionic strength or pH. The amount of extraction medium used is somewhat critical in that sufficient medium must be present to allow approximately immediate extraction of the solvent out of the microdroplets. Accordingly, the volume of the extraction medium will depend on the solvent used to dissolve the wall material and its solubility in the extraction medium. Generally, the volume of the extraction medium should be at least the volume needed to dissolve all of the solvent out of the microdroplets, preferably a volume 10-fold or higher.

[0025] After extraction of all or almost all of the solvent from the microdroplets (generally within 15 to 30 minutes), the hardened microcapsules or microspheres are collected by centrifugation, filtration, or the like. One advantage to this process is that it can be a discontinuous or a continuous process.

[0026] Having generally described the invention, certain processing parameters will now be described that affect the structure and properties of the final product. Generally, when solid compounds and in certain instances liquids are microencapsulated, the resultant product obtained are microspheres. Generally, when liquids are encapsulated, the liquid coalesces inside of the microdroplet resulting in a microcapsule product. If the liquid is removed, for example, by vacuum drying, from the microcapsule product, microbubbles can be obtained.

[0027] One of the advantages of the present invention is that solid agents can be encapsulated with the final product comprising microcapsules that demonstrate zero-order or near zero-order release kinetics. This is achieved by encapsulating very water-soluble agents. Especially during formation of the emulsion, very water-soluble agents attract water into the microdroplet, which coalesces and keeps the wall-forming material from precipitating as a matrix throughout the microdroplet. Obviously, to obtain a microcapsule, the solid agent being encapsulated must have sufficient water solubility to attract water into the microdroplet. If the active agent does not have the proper solubility, then coencapsulation of the agent with a highly water-soluble auxiliary compound, such as a sugar or salt, can result in the formation of microcapsules. Or, if only the sugar or salt is encapsulated and subsequently removed from the microcapsules, microbubbles can be obtained.

[0028] Because water-soluble agents, such as peptides and proteins, do not diffuse through hydrophobic wall-forming material such as the lactide/glycolide copolymers, pores must be created in the microcapsule or microsphere membrane to allow these agents to diffuse out for controlled-release applications. Several factors will affect the porosity obtained. The amount of agent that is encapsulated affects the porosity of microspheres. Obviously, higher-loaded microspheres (i.e., greater than about 20 wt %, and preferably between 20 wt % and 80 wt %) will be more porous than microspheres

containing smaller amounts of agent (i.e., less than about 20 wt %) because more regions of drug are present throughout the microspheres. The ratio of agent to wall-forming material that can be incorporated into the microspheres can be as low as 0.1% to as high as 80%. Obviously, the loading that can be obtained for specific agents will depend to some extent on the physical properties of the agent and the desired application for the microsphere formulation.

[0029] The solvent used to dissolve the wall-forming material will also affect the porosity of the membrane. Microspheres or microcapsules prepared from a solvent such as ethyl acetate will be more porous than microspheres or microcapsules prepared from chloroform. This is due to the higher solubility of water in ethyl acetate than in chloroform. More specifically, during the emulsion step, no solvent is removed from the microdroplets because the process medium is saturated with solvent. Water, however, can dissolve in the solvent of the microdroplets during the emulsion step of the process. By selecting the appropriate solvent or cosolvents, the amount of continuous process medium that will dissolve in the microdroplets can be controlled, which will affect the final porosity of the membrane and the internal structure of the microspheres or microcapsules.

[0030] Another factor that will affect the porosity of the membrane is the initial concentration of the wall material/excipient in the solvent. High concentrations of wall material in the solvent result in less porous membranes than do low concentrations of wall material/excipient. Also, high concentrations of wall material/excipient in the solvent improve the encapsulation efficiency of water-soluble compounds because the viscosity of the solution is higher. Generally, the concentration of wall-forming material/excipient in the solvent will range from about 3% to about 40%, depending on the physical/chemical properties of the wall material/excipient such as the molecular weight of the wall-forming material and the solvent used.

[0031] Having generally described the invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purpose of illustration.

EXAMPLE 1

[0032] The following procedure was used to encapsulate choline chloride in polystyrene using an aqueous process medium. The solubility of choline chloride in water is greater than 3 grams per milliliter.

[0033] First, a polymer solution was prepared by dissolving 1.0 g of polystyrene (Type 6850, Dow Chemical Co., Midland, MI) in 9.0 g of methylene chloride. Next, 1.0 g of choline chloride was dissolved in 250 μ L deionized water. The polystyrene solution was transferred to a 100 x 20 mm test tube. While the polystyrene solution was being vortexed, the choline chloride solution was added dropwise to the test tube. The choline chloride was homogeneously dispersed in the polystyrene solution by homogenization using a Brinkmann Polytron (Model 10, PTA-10S probe, speed setting of 5, Brinkmann Instruments Co., Westbury, NY).

[0034] A 100-mL resin kettle was fitted with a truebore stirrer and a 38.1 m.m. (1.5-in.) TEFLON turbine impeller. Next, 50 mL of 4 wt % aqueous poly(vinyl alcohol) (PVA) was saturated with 0.8 g of methylene chloride and transferred to the resin kettle. The polystyrene/choline chloride dispersion was poured directly into the PVA processing medium. During this transfer, the PVA solution was being stirred at about 550 rpm. After the resulting oil-in-water emulsion had stirred in the resin kettle for 1 min, the contents of the resin kettle were transferred all at once into 3.5 L of deionized water contained in a 4-L beaker and being stirred at about 750 rpm with a 50.8 m.m. (2-in.) stainless steel impeller. The resultant microspheres were stirred in the deionized water for about 25 min., collected over a 203.2 m.m. (8-in) diameter, 45-micron mesh stainless steel sieve, rinsed with 4 L of deionized water, and dried for 48 hours at ambient temperature in a vacuum chamber.

[0035] The final microsphere product consisted of free flowing spherical particles having diameters of about 45 to 250 microns and containing about 40 to 45 wt % choline chloride.

EXAMPLE 2

[0036] A 15 wt % polymer solution was prepared by dissolving 0.75 g of 50:50 poly(DL-lactide-co-glycolide) (DL-PLG) in 4.25 g of methylene chloride. Next 30 mg of formalinized staphylococcal enterotoxin B (SEB) was dissolved in 110 μ L deionized water. The organic polymer solution was transferred to a 16 x 100 mm test tube and the SEB toxoid solution was then introduced dropwise into the polymer solution while the latter was being agitated with a Vortex mixer. This mixture was then homogenized with a Polytron homogenizer to ensure that the SEB toxoid was homogeneously dispersed in the DL-PLG solution.

[0037] In a separate container, 300 mL of 1.5 wt % aqueous carboxymethyl cellulose that had been saturated with methylene chloride was equilibrated to 19.0 \pm 1.0 $^{\circ}$ C. The standard head, equipped with the emulsor screen, of a Silverson Laboratory Mixer was positioned below the surface of the carboxymethyl cellulose solution and the stir rate of the mixer was adjusted to approximately 4200 rpm.

[0038] The SEB toxoid/DL-PLG mixture was dispersed as microdroplets in the aqueous carboxymethyl cellulose. The resulting oil-in-water emulsion was stirred for about 3 minutes, after which the emulsion was transferred all at once

to 3.5 L of deionized water contained in a glass beaker and being stirred at about 500 rpm with a 50.8 m.m. (2-in). stainless steel impeller. The resultant microspheres were stirred in the purified water for about 20 min, collected over a 0.22- μ m filter, and dried for 48 h in a vacuum chamber.

[0039] The resultant microsphere product consisted of spherical particles about 1 to 10 μ m comprising 2.7 wt % of SEB toxoid in poly(DL-lactide-co-glycolide).

EXAMPLE 3 (for reference, not within the invention)

[0040] Approximately 2.5 g of poly(DL-lactide)(DL-PL) was dissolved in the appropriate quantity of methylene chloride to prepare an 11.1 wt % polymer solution. After the polymer was completely dissolved, a predetermined quantity of testosterone propionate was added and allowed to dissolve. This polymer/drug solution was then poured into a 1-L resin kettle containing 400 g of 5.0 wt % PVA. The PVA was being stirred at about 750 by a 63.5 m.m. (2.5 in) TEFLON impeller driven by a Fisher Stedi-speed motor. The PVA was also saturated with 7 mL of methylene chloride prior to the addition of the polymer/drug solution. The resulting emulsion was allowed to stir for 7 min., after which the resin kettle contents were transferred all at once to 12.0 L of stirring deionized water. The microspheres were stirred in the deionized water for approximately 30 min and then were collected over 45- μ m and 212- μ m stainless steel mesh sieves arranged in series. The microspheres were rinsed with additional deionized water and allowed to air dry.

[0041] A similar batch of testosterone propionate microspheres was made with a 20.6 wt % polymer solution. The in vitro release rates for these two batches are shown below, demonstrating that the concentration of the polymer solution can be used to manipulate the release properties of microspheres. That is, higher polymer concentration gave slower releasing microspheres.

Polymer solution concentration wt %	Core loading, wt% testosterone propionate	In vitro release, % at time					
		1h	1d	2d	3d	6d	8d
11.1	39.5	8.2	29.3	38.5	45.2	59.3	70.7
20.6	40.2	2.0	9.0	13.3	16.7	22.8	30.2

EXAMPLE 4 (for reference, not within the invention)

[0042] A 0.5-g amount of etretinate [(All-E)-9-(4-methoxy-2,3,6-trimethyl)phenyl-3,7-dimethyl-2,4,6,8-nonatetraenoic acid, ethyl ester] and 0.33 g of 50:50 DL-PLG were dissolved in 12.4 g of methylene chloride. (Due to the photosensitivity of etretinate, all steps in the process were done in the dark.) The organic solution was dispersed as microdroplets in 300 g of 10 wt % aqueous poly(vinyl alcohol). The emulsion was obtained by the addition of the organic solution to a rapidly stirring solution of aqueous poly(vinyl alcohol) in a glass container. A Silverson Heavy Duty Laboratory Mixer was used to stir the emulsion.

[0043] After the organic microdroplets were stirred in the poly(vinyl alcohol) solution for 5 min to form a stable oil-in-water emulsion, the emulsion was transferred to 4 L of stirring, deionized water. The resultant microspheres were stirred in the deionized water for 30 min, separated from the poly(vinyl alcohol) by centrifugation, and collected by lyophilization.

[0044] The final product consisted of free-flowing particles with diameters from 0.5 to 5 μ m containing 40 wt % etretinate in poly (DL-lactide-co-glycolide).

EXAMPLE 5 (for reference)

[0045] A 12 wt % polymer solution was prepared by dissolving 1.0 g of 50:50 DL-PLG in 7.3 g of methylene chloride. Next 0.4 g of micronized cefazolin sodium was dispersed in the polymer solution. The cefazolin/polymer mixture was dispersed as microdroplets in 100 g of 6 wt % of aqueous poly(vinyl alcohol) saturated with 2.4 g of methylene chloride. The emulsion was obtained by the addition of the cefazolin/polymer mixture to the aqueous poly(vinyl alcohol) solution while stirring the PVA at about 1000 rpm in a resin kettle. A TEFLON turbine impeller driven by a Fisher Stedi-Speed motor was used to stir the emulsion. As the emulsion was stirred, water entered the microdroplets (as observed under a microscope) and coalesced. After a stable oil-in-water emulsion had formed, the contents of the resin kettle were transferred all at once to 3.5 L of water stirring at 600 rpm to extract the methylene chloride from the microcapsules. After the extraction was complete, the microcapsules were allowed to settle. The microcapsules were collected over sieves and then washed with at least 3 L of water. The microcapsules were placed in a vacuum at ambient temperatures to dry for at least 24 h.

[0046] The resultant microcapsule product consisted of spherical particles with a central core of cefazolin sodium encapsulated in an outer DL-PLG membrane.

EXAMPLE 6 (for reference)

[0047] A 15 wt % polymer solution was prepared by dissolving 3 g of 50:50 DL-PLG in 17 g of methylene chloride. Next, 0.4 g of LHRH was dispersed in the polymer solution while the latter was being agitated with a Polytron homogenizer. The LHRH/DL-PLG mixture was dispersed as microdroplets in 200 g of 5 wt % poly(vinyl alcohol) (PVA) which had previously been saturated by adding 3.6 g of methylene chloride to the PVA. The emulsion was obtained by the addition of the LHRH/DL-PLG mixture to the PVA process medium being stirred at 1060 rpm and contained in a resin kettle. A TEFLON turbine impeller driven by a Fisher Stedi-Speed motor was used to stir the emulsion.

[0048] After a stable oil-in-water emulsion was formed, the emulsion was transferred all at once to 7 L of stirring deionized water to extract the methylene chloride. The resultant microspheres were allowed to harden in the water bath for 15 min, collected over 45 and 150- μ m sieves, washed with approximately 2 L of deionized water to remove any residual PVA, and air dried for 48 h.

[0049] The final product consisted of a free-flowing powder with diameters ranging from 45 to 150 μ m comprising 8.2 wt % LHRH encapsulated in DL-PLG.

EXAMPLE 7 (for reference, not within the invention)

[0050] An 8 wt % ethyl cellulose solution was prepared by dissolving 1 g of Ethocel (Premium grade, Standard ethoxy content, 20 viscosity, Dow Chemical Co., Midland, MI) in 11.5 g of methylene chloride. Next, 0.5 g of mannitol was dissolved in 3 mL of deionized water. The ethyl cellulose solution was transferred to a 100 x 20 mm test tube. While the ethyl cellulose solution was being agitated with a vortex mixer, the mannitol solution was added dropwise to the tube. A Brinkmann Polytron (Model 10, m PTA-10S probe, speed setting of 5, Brinkmann Instruments Co., Westbury, NY) was then used to homogenize the solution.

[0051] A 453.6 g. (16-oz.), wide-mouth jar was used to contain 300 mL of a 5 wt % aqueous solution of (PVA). This solution was saturated with 4.8 g of methylene chloride. Throughout the procedure the PVA solution was maintained at 19 °C. A Silverson Laboratory Mixer Emulsifier (Model L2R, equipped with a medium emulsor screen, Silverson Machines Limited, Waterside, Chesham, Buckinghamshire, England) was used to stir the PVA solution at 4000 rpm. Using a 10 mm bore funnel, the ethyl cellulose/mannitol solution was added to the stirring PVA. After 4 min, the contents of the jar were transferred all at once to 3 L of deionized water stirring at about 750 rpm. The methylene chloride was extracted into the water along with the mannitol to give microbubbles. The microbubbles were stirred for 1 h to ensure that all of the mannitol and methylene chloride was removed. The microbubbles were then collected.

[0052] The final microbubble product consists of spherical particles 1 to 10 microns in diameter with hollow interiors.

EXAMPLE 8 (for reference, not within the invention)

[0053] An 11.9 wt % polymer solution was prepared by dissolving 0.5 g of 52:48 poly(DL-lactide-co-glycolide) (DL-PLG) (inherent viscosity of 0.73 dL/g. measured at a polymer concentration of 0.5 g/dL in hexafluoroisopropanol at 30°C using a Cannon viscometer) in 3.7 g of methylene chloride. Next, 0.125 g of a mixture comprising 1 part by weight of interleukin-2 conjugated to a polyol polymer (PEG-IL-2) and 20 parts by weight of human serum albumin was weighed into a 16 x 75 mm test tube. The DL-PLG solution was added to the test tube, and the mixture was homogenized three times for 30 sec, with 15-sec intervals between homogenizations. The homogenization was done with a Brinkman Polytron (Model 10, PTA-10S probe, speed setting of 6).

[0054] A 200 mL resin kettle was fitted with a truebore stirrer and a 38.1 m.m. (1.5-in). TEFLON turbine impeller. Next, 150 mL of 6 wt % aqueous poly(vinyl alcohol) was saturated with 2.4 g of methylene chloride and transferred to the resin kettle. The homogenized organic mixture was dispersed as microdroplets in the poly(vinyl alcohol). The dispersion was obtained by the addition of the organic mixture beneath the surface of the poly(vinyl alcohol) solution. During this transfer, the poly(vinyl alcohol) was being stirred at about 1000 rpm. The dispersion was stirred in the resin kettle for 5 min resulting in the formation of a stable oil-in-water emulsion.

[0055] After a stable oil-in-water emulsion was prepared, the contents of the resin kettle were quickly transferred to 10 L of deionized water contained in a 12-L beaker and being stirred at about 800 rpm with a 50.8 m.m. (2-in.) stainless steel impeller. The resultant microspheres were stirred in the deionized water for about 15 min, collected over an 203.2 m.m. (8-in) diameter, 45- μ m stainless steel sieve, rinsed with 4 L of deionised water, and dried for 48-h at ambient temperature in a vacuum chamber. The final product consisted of free-flowing particles with diameters from 45 to 200 μ m comprising 15.6 wt % of the PEG-IL-2/HSA mixture in poly(DL-lactide-co-glycolide).

Claims

1. A method of microencapsulating an agent, to form a microencapsulated product, comprising:

- a) dispersing an effective amount of the agent in a solvent containing a dissolved wall-forming material to form a dispersion;
- b) combining the dispersion with an effective amount of a continuous process medium to form an emulsion that contains the process medium and microdroplets comprising the agent, the solvent and the wall-forming material within 30 seconds; and
- c) immediately within up to three minutes after the formation of the emulsion adding all at once the emulsion to an effective amount of an extraction medium to extract the solvent from the microdroplets to form the microencapsulated product, wherein the solvent has a solubility in the extraction medium from about 1 part per 100 to about 25 parts per 100.

2. A method according to Claim 1, wherein the dispersing step comprises dissolving the agent in the solvent.

3. A method according to any preceding Claim, wherein the solvent is immiscible with the process medium.

4. A method according to any preceding Claim, wherein the process medium is water.

5. A method according to any one of claims 1 to 3, wherein the process medium is an organic solvent.

6. A method according to Claim 5, wherein the process medium is an oil.

7. A method according to any preceding Claim, wherein the process medium contains a surfactant.

8. A method according to Claim 7, wherein the surfactant is present in the process medium from about 0.1% to about 20% by weight.

9. A method according to any preceding Claim, and further comprising the step of saturating the process medium with the solvent prior to adding the dispersant to the continuous process medium.

10. A method according to any preceding Claim, and further comprising preventing evaporation of the solvent from the microdroplets.

11. A method according to any preceding Claim, wherein the extraction medium is water.

12. A method according to any one of claims 1 to 10, wherein the extraction medium is an organic solvent.

13. A method according to Claim 12, wherein the extraction medium is an oil.

14. A method according to any preceding Claim, and further comprising dissolving an effective amount of a salt in the extraction medium to adjust its ionic strength.

15. A method according to any preceding Claim, and further comprising controlling the pH of the extraction medium by adding an acid or base.

16. A method according to any preceding Claim, and further comprising separating the microencapsulated product from the extraction medium.

17. A method according to any preceding Claim, wherein the agent is a water soluble compound.

18. A method according to any preceding Claim, wherein the agent has a solubility of greater than 10 milligrams per millilitre in the continuous process medium.

19. A method according to any preceding Claim, wherein the agent has a solubility of greater than 10 milligrams per millilitre in the extraction medium.

20. A method according to any preceding Claim, wherein the ratio of the agent to the wall forming material in the dispersion is high to control the porosity of the microencapsulated product.
21. A method according to any preceding Claim, wherein the percentage of the agent to the wall forming material in the dispersion is greater than about 20 wt %.
22. A method according to Claim 21, wherein the percentage of the agent to the wall forming material in the dispersion is from about 20 wt % to about 80 wt %.
23. A method according to any one of Claims 1 to 19, wherein the percentage of the agent to the wall forming material in the dispersion is low to control the porosity of the microencapsulated product.
24. A method according to Claim 23, wherein the percentage of the agent to the wall forming material in the dispersion is less than about 20 wt %.
25. A method according to any preceding Claim, wherein the continuous process medium is soluble in the solvent to control the porosity of the microencapsulated product.
26. A method according to Claim 25, wherein the continuous process medium has a solubility of from about 2% to about 25% in the solvent.
27. A method according to Claim 22, wherein the continuous process medium has a solubility of less than about 2% in the solvent.
28. A method according to any preceding Claim, wherein the solvent is selected from ethyl acetate, diethyl carbonate, chloroform and methyl chloride and the continuous process medium is water.
29. A method according to any preceding Claim, wherein the agent is soluble in the continuous process medium.
30. A method according to Claim 29, wherein the agent has a solubility greater than 100 mg/ml in the continuous process medium.
31. A method according to any preceding Claim, wherein the agent has a solubility greater than 100 mg/ml in the extraction medium.
32. A method according to any preceding Claim, further comprising the step prior to step b) of mixing a water soluble auxiliary compound with the agent.
33. A method according to Claim 32, wherein the auxiliary compound has a solubility greater than 100 mg/ml in the continuous process medium.
34. A method according to Claim 32 or 33, wherein the auxiliary compound has a solubility greater than 100 mg/ml in the extraction medium.
35. A method according to Claim 33 or 34, wherein the auxiliary compound has a solubility greater than 1 gram/ml in the continuous process medium.
36. A method according to any one of Claims 33 to 36, wherein the auxiliary compound has a solubility greater than 1 gram/ml in the, extraction medium.
37. A method according to any preceding Claim, wherein the agent is a solid compound.
38. A method according to any one of Claims 1 to 36, wherein the agent is a liquid.
39. A method according to any one of Claims 32 to 37, wherein the agent is a solid compound.
40. A method according to any preceding Claim, wherein the percentage of wall forming material to solvent in the dispersion is between about 3 wt % and 40 wt %.

41. A method according to any preceding Claim, wherein the wall-forming material is present at a concentration greater than 20 wt % in the solvent.
42. A method according to any one of Claims 1 to 40, wherein the wall-forming material is present at a concentration less than 20 wt % in the solvent.
43. A method according to claim 1, wherein the method comprises a continuous process.
44. A method according to claim 1, wherein the microencapsulated agent is an analgesic, anaesthetic, anorexic, antiarthritic, antiasthmatic, antibiotic, antifungal, antiviral, anticancer agent, anticoagulant, anticonvulsant, antidepressant, antihistamine, hormone, tranquillizer, antispasmodic, vitamin, mineral, cardiovascular agent, enzyme, peptide, protein, prostaglandin, nucleic acid, carbohydrate, fat, narcotic, psychotherapeutic, antimalarial, L-dopa, diuretic, antiulcer drug, or immunological agent.
45. A method according to claim 1, wherein the microencapsulated agent is an adhesive, pesticide, fragrance, anti-foulant, dye, salt, oil, ink, cosmetic, catalyst, detergent, curing agent, flavour, food, fuel, herbicide, metal, paint, photographic agent, biocide, pigment, plasticizer, propellant, solvent, stabilizer or polymer additive.
46. A method according to claim 1, wherein the wall-forming material is poly(lactide), poly(glycolide), poly(caprolactone), poly(hydroxybutyrate) or copolymers thereof.
47. A method according to claim 1, wherein the product comprises a central core of agent surrounded by an outer membrane.
48. A method according to any preceding claim, wherein the agent is soluble in the continuous process medium, the extraction medium, or both media.
49. A method according to claim 48, wherein the agent is water soluble, the continuous process medium is aqueous and the extraction medium is aqueous.

Patentansprüche

1. Verfahren zur Mikroverkapselung eines Mittels zur Bildung eines mikroverkapselten Produkts, bei dem man:
- (a) eine wirksame Menge des Mittels in einem Lösungsmittel, das ein gelöstes wandbildendes Material enthält, zur Bildung einer Dispersion dispergiert;
- (b) die Dispersion mit einer wirksamen Menge eines kontinuierlichen Arbeitsmediums zur Bildung einer Emulsion, welche das Arbeitsmedium sowie das Mittel, das Lösungsmittel und das wandbildende Material enthaltende Mikrotropfen enthält, innerhalb von 30 Sekunden vereinigt und
- (c) sofort innerhalb von bis zu 3 Minuten nach der Bildung der Emulsion die Emulsion auf einmal zu einer wirksamen Menge eines Extraktionsmittels zugibt zur Extraktion des Lösungsmittels aus den
- (d) Mikrotropfen, um das mikroverkapselte Produkt zu bilden, wobei das Lösungsmittel in dem Extraktionsmedium eine Löslichkeit von etwa einem Teil von 100 bis etwa 25 Teilen von 100 hat:
2. Verfahren nach Anspruch 1, bei dem der Dispergierschritt das Auflösen des Mittels im Lösungsmittel beinhaltet.
3. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Lösungsmittel nicht mit dem Arbeitsmedium mischbar ist.
4. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Arbeitsmedium Wasser ist.
5. Verfahren nach einem der Ansprüche 1 bis 3, bei dem das Arbeitsmedium ein organisches Lösungsmittel ist.
6. Verfahren nach Anspruch 5, bei dem das Arbeitsmedium ein Öl ist.

7. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Arbeitsmedium ein Tensid enthält.
8. Verfahren nach Anspruch 7, bei dem das Tensid im Arbeitsmedium in einer Menge von etwa 0,1 Gew.-% bis etwa 20 Gew.-% vorliegt.
- 5 9. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man vor der Zugabe des Dispergiemittels zum kontinuierlichen Arbeitsmedium das Arbeitsmedium mit dem Lösungsmittel sättigt.
- 10 10. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man das Verdampfen des Lösungsmittels aus den Mikrotropfen verhindert.
11. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Extraktionsmittel Wasser ist.
12. Verfahren nach einem der Ansprüche 1 bis 10, bei dem das Extraktionsmittel ein organisches Lösungsmittel ist.
- 15 13. Verfahren nach Anspruch 12, bei dem das Extraktionsmittel ein Öl ist.
14. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man zur Einstellung der Ionenstärke eine wirksame Menge eines Salzes im Extraktionsmittel auflöst.
- 20 15. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man den pH-Wert des Extraktionsmittels durch Zugabe einer Säure oder einer Base reguliert.
- 25 16. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man das mikroverkapselte Produkt vom Extraktionsmittel abtrennt.
17. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel eine wasserlösliche Verbindung ist.
- 30 18. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel eine Löslichkeit von mehr als 10 Milligramm pro Milliliter im kontinuierlichen Arbeitsmedium aufweist.
19. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel eine Löslichkeit von mehr als 10 Milligramm pro Milliliter im Extraktionsmittel aufweist.
- 35 20. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Verhältnis von Mittel zu wandbildendem Material in der Dispersion zur Regulierung der Porosität des mikroverkapselten Produkts hoch ist.
21. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das prozentuale Verhältnis des Mittels zum wandbildenden Material in der Dispersion höher als etwa 20 Gew.-% ist.
- 40 22. Verfahren nach Anspruch 21, bei dem das prozentuale Verhältnis des Mittels zum wandbildenden Material in der Dispersion etwa 20 Gew.-% bis etwa 80 Gew.-% beträgt.
- 45 23. Verfahren nach einem der Ansprüche 1 bis 19, bei dem man für eine niedrige Porosität des mikroverkapselten Produkts ein niedriges prozentuales Verhältnis des Mittels zum wandbildenden Material in der Dispersion wählt.
24. Verfahren nach Anspruch 23, bei dem das prozentuale Verhältnis des Mittels zum wandbildenden Material in der Dispersion niedriger als etwa 20 Gew.-% ist.
- 50 25. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man für eine hohe Porosität des mikroverkapselten Produkts ein in dem Lösungsmittel lösliches kontinuierliches Arbeitsmedium wählt.
26. Verfahren nach Anspruch 25, bei dem das kontinuierliche Arbeitsmedium eine Löslichkeit von etwa 2 % bis etwa 25 % im Lösungsmittel aufweist.
- 55 27. Verfahren nach Anspruch 25, bei dem das kontinuierliche Arbeitsmedium eine Löslichkeit von weniger als etwa 2 % im Lösungsmittel aufweist.

28. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man das Lösungsmittel aus Essigsäureethylester, Diethylcarbonat, Chloroform und Methylchlorid auswählt und das kontinuierliche Arbeitsmedium Wasser ist.
29. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel im kontinuierlichen Arbeitsmedium löslich ist.
30. Verfahren nach Anspruch 29, bei dem das Mittel eine Löslichkeit von mehr als 100 mg/ml im kontinuierlichen Arbeitsmedium aufweist.
31. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel eine Löslichkeit von mehr als 100 mg/ml im Extraktionsmittel aufweist.
32. Verfahren nach einem der vorhergehenden Ansprüche, bei dem man vor Schritt b) das Mittel mit einer wasserlöslichen Hilfsverbindung vermischt.
33. Verfahren nach Anspruch 32, bei dem die Hilfsverbindung eine Löslichkeit von mehr als 100 mg/ml im kontinuierlichen Arbeitsmedium aufweist.
34. Verfahren nach Anspruch 32 oder 33, bei dem die Hilfsverbindung eine Löslichkeit von mehr als 100 mg/ml im Extraktionsmedium aufweist.
35. Verfahren nach Anspruch 33 oder 34, bei dem die Hilfsverbindung eine Löslichkeit von mehr als 1 Gramm/ml im kontinuierlichen Arbeitsmedium aufweist.
36. Verfahren nach einem der Ansprüche 33 bis 35, bei dem die Hilfsverbindung eine Löslichkeit von mehr als 1 Gramm/ml im Extraktionsmedium aufweist.
37. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel ein Feststoff ist.
38. Verfahren nach einem der Ansprüche 1 bis 36, bei dem das Mittel eine Flüssigkeit ist.
39. Verfahren nach einem der Ansprüche 32 bis 37, bei dem das Mittel ein Feststoff ist.
40. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das prozentuale Verhältnis des wandbildenden Materials zum Lösungsmittel in der Dispersion etwa 3 Gew.-% bis 40 Gew.-% beträgt.
41. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das wandbildende Material in einer Konzentration von mehr als 20 Gew.-% im Lösungsmittel vorliegt.
42. Verfahren nach einem der Ansprüche 1 bis 40, bei dem das wandbildende Material in einer Konzentration von weniger als 20 Gew.-% im Lösungsmittel vorliegt.
43. Verfahren nach Anspruch 1, bei dem das Verfahren ein kontinuierliches Verfahren beinhaltet.
44. Verfahren nach Anspruch 1, bei dem das mikroverkapselte Mittel ein Analgetikum, ein Anästhetikum, ein Appetitzügler, ein Antiarthritikum, ein Antiasthmikum, ein Antibiotikum, ein Pilzbefallverhütungsmittel, ein Antivirusemittel, ein antikarzinogenes Mittel, ein Antikoagulationsmittel, ein Antikrampfmittel, ein Antidepressivum, ein Antihistamin, ein Hormon, ein Beruhigungsmittel, ein Antispastikum, ein Vitamin, ein Mineral, ein Kreislaufrmittel, ein Enzym, ein Peptid, ein Protein, ein Prostaglandin, eine Nukleinsäure, ein Kohlenhydrat, ein Fett, ein Narkotikum, ein psychotherapeutisches Mittel, ein Antimalariamittel, L-Dopa, ein Diuretikum, ein antiulcerogenes Mittel oder ein immunologisches Mittel ist.
45. Verfahren nach Anspruch 1, bei dem das mikroverkapselte Mittel ein Klebstoff, ein Pestizid, ein Riechstoff, ein Antifoulingmittel, ein Farbstoff, ein Salz, ein Öl, eine Tinte, ein Schönheitspflegemittel, ein Katalysator, ein Wasch- oder Reinigungsmittel, ein Härtungsmittel, ein Aromastoff, ein Lebensmittel, ein Brenn- oder Kraftstoff, ein Herbizid, ein Metall, ein Anstrichmittel, ein photographisches Agens, ein Biozid, ein Pigment, ein Weichmacher, ein Treibmittel oder -stoff, ein Lösungsmittel, ein Stabilisator oder ein Polymeradditiv ist.

46. Verfahren nach Anspruch 1, bei dem das wandbildende Material Poly(lactid), Poly(glycolid), Poly(caprolacton), Poly(hydroxybutyrat) oder deren Copolymere ist.
47. Verfahren nach Anspruch 1, bei dem das Produkt aus einem von einer äußeren Membran umgebenen zentralen Kern aus dem Mittel besteht.
48. Verfahren nach einem der vorhergehenden Ansprüche, bei dem das Mittel im kontinuierlichen Arbeitsmedium, im Extraktionsmittel oder in beiden Medien löslich ist.
49. Verfahren nach Anspruch 48, bei dem das Mittel wasserlöslich, das kontinuierliche Arbeitsmedium wässrig und das Extraktionsmittel wässrig ist.

Revendications

1. Procédé de microencapsulation d'un agent, de façon à former un produit microencapsulé comprenant :
 - a) la dispersion d'une quantité efficace de l'agent dans un solvant contenant un matériau formateur de paroi dissout de façon à former une dispersion,
 - b) la combinaison de la dispersion avec une quantité efficace d'un milieu d'élaboration continu de façon à former une émulsion qui contient le milieu d'élaboration et des microgouttelettes comprenant l'agent, le solvant et le matériau formateur de paroi en moins de 30 s, et
 - c) immédiatement, dans les trois minutes qui suivent la formation de l'émulsion, l'addition en une seule fois de l'émulsion à une quantité efficace d'un milieu d'extraction de façon à extraire le solvant des microgouttelettes de manière à former le produit microencapsulé, le solvant ayant une solubilité dans le milieu d'extraction comprise entre environ 1 partie pour 100 et environ 25 parties pour 100.
2. Procédé selon la revendication 1, dans lequel l'étape de dispersion comprend la dissolution de l'agent dans le solvant.
3. Procédé selon l'une quelconque des revendications précédentes, dans lequel le solvant n'est pas miscible avec le milieu d'élaboration.
4. Procédé selon l'une quelconque des revendications précédentes, dans lequel le milieu d'élaboration est l'eau.
5. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel le milieu d'élaboration est un solvant organique.
6. Procédé selon la revendication 5, dans lequel le milieu d'élaboration est une huile.
7. Procédé selon l'une quelconque des revendications précédentes, dans lequel le milieu d'élaboration contient un agent tensioactif.
8. Procédé selon la revendication 7, dans lequel l'agent tensioactif est présent dans le milieu d'élaboration en proportion d'environ 0,1 % à environ 20 % en poids.
9. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape consistant à saturer le milieu d'élaboration avec le solvant avant d'ajouter le dispersant au milieu d'élaboration continu.
10. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape consistant à empêcher l'évaporation du solvant à partir des micro-gouttelettes.
11. Procédé selon l'une quelconque des revendications précédentes, dans lequel le milieu d'extraction est l'eau.
12. Procédé selon l'une quelconque des revendications 1 à 10, dans lequel le milieu d'extraction est un solvant organique.
13. Procédé selon la revendication 12, dans lequel le milieu d'extraction est une huile.

14. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape consistant à dissoudre une quantité effective d'un sel dans le milieu d'extraction de façon à ajuster sa concentration ionique.
- 5 15. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape consistant à contrôler le pH du milieu d'extraction en ajoutant un acide ou une base.
16. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape consistant à séparer le produit microencapsulé du milieu d'extraction.
- 10 17. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent est un composé soluble dans l'eau.
18. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent présente une solubilité supérieure à 10 milligrammes par millilitre dans le milieu d'élaboration continu.
- 15 19. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent présente une solubilité supérieure à 10 milligrammes par millilitre dans le milieu d'extraction.
- 20 20. Procédé selon l'une quelconque des revendications précédentes, dans lequel le rapport de l'agent au matériau formateur de paroi dans la dispersion est élevé de façon à contrôler la porosité du produit microencapsulé.
21. Procédé selon l'une quelconque des revendications précédentes, dans lequel le pourcentage de l'agent par rapport au matériau formateur de paroi dans la dispersion est supérieur à environ 20 % en poids.
- 25 22. Procédé selon la revendication 21, dans lequel le pourcentage de l'agent au matériau formateur de paroi dans la dispersion est compris entre environ 20 % en poids et environ 80 % en poids.
23. Procédé selon l'une quelconque des revendications 1 à 19, dans lequel le pourcentage de l'agent au matériau formateur de paroi dans la dispersion est faible de façon à contrôler la porosité du produit microencapsulé.
- 30 24. Procédé selon la revendication 23, dans lequel le pourcentage de l'agent au matériau formateur de paroi dans la dispersion est inférieur à environ 20 % en poids.
25. Procédé selon l'une quelconque des revendications précédentes, dans lequel le milieu d'élaboration continu est soluble dans le solvant de façon à contrôler la porosité du produit microencapsulé.
- 35 26. Procédé selon la revendication 25, dans lequel le milieu d'élaboration continu présente une solubilité comprise entre environ 2 % et environ 25 % dans le solvant.
- 40 27. Procédé selon la revendication 25, dans lequel le milieu d'élaboration continu présente une solubilité inférieure à environ 2 % dans le solvant.
28. Procédé selon l'une quelconque des revendications précédentes, dans lequel le solvant est choisi parmi l'acétate d'éthyle, le carbonate de diéthyle, le chloroforme et le chlorure de méthyle, et le milieu d'élaboration continu est l'eau.
- 45 29. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent est soluble dans le milieu d'élaboration continu.
- 50 30. Procédé selon la revendication 29, dans lequel l'agent a une solubilité supérieure à 100 mg/ml dans le milieu d'élaboration continu.
31. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent présente une solubilité supérieure à 100 mg/ml dans le milieu d'extraction.
- 55 32. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre l'étape avant l'étape b) consistant à mélanger un composé auxiliaire soluble dans l'eau avec l'agent.

33. Procédé selon la revendication 32, dans lequel le composé auxiliaire présente une solubilité supérieure à 100 mg/ml dans le milieu d'élaboration continu.
34. Procédé selon la revendication 32 ou la revendication 33, dans lequel le composé auxiliaire présente une solubilité supérieure à 100 mg/ml dans le milieu d'extraction.
35. Procédé selon la revendication 34 ou la revendication 34, dans lequel le composé auxiliaire présente une solubilité supérieure à 1 g/ml dans le milieu d'élaboration continu.
36. Procédé selon l'une quelconque des revendications 33 à 35, dans lequel le composé auxiliaire présente une solubilité supérieure à 1 g/ml dans le milieu d'extraction.
37. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent est un composé solide.
38. Procédé selon l'une quelconque des revendication 1 à 36, dans lequel l'agent est un liquide.
39. Procédé selon l'une quelconque des revendications 32 à 35, dans lequel l'agent est un composé solide.
40. Procédé selon l'une quelconque des revendications précédentes, dans lequel le pourcentage du matériau formateur de paroi par rapport au solvant dans la dispersion est compris entre environ 3 % en poids et 40 % en poids.
41. Procédé selon l'une quelconque des revendications précédentes, dans lequel le matériau formateur de paroi est présent sous une concentration supérieure à 20 % en poids dans le solvant.
42. Procédé selon l'une quelconque des revendications 1 à 40, dans lequel le matériau formateur de paroi est présent sous une concentration inférieure à 20 % en poids dans le solvant.
43. Procédé selon la revendication 1, dans lequel le procédé comprend un processus continu.
44. Procédé selon la revendication 1, dans lequel l'agent microencapsulé est un analgésique, un anesthésique, un anorexique, un anti-arthritique, un anti-asthmatique, un antibiotique, un antifongique, un anti-viral, un agent anti cancer, un anti-coagulant, un anti-convulsant, un antidépresseur, un anti-histaminique, une hormone, un tranquillisant, un anti-spasmodique, une vitamine, un minéral, un agent cardiovasculaire, une enzyme, une peptide, une protéine, une prostaglandine, un acide nucléique, un hydrate de carbone, une matière grasse, un narcotique, un agent psychothérapeutique, un anti-malarique, un L-dopa, un diurétique, un médicament anti ulcère ou agent immunologique.
45. Procédé selon la revendication 1, dans lequel l'agent microencapsulé est un adhésif, un pesticide, un parfum, un agent préservatif, une teinture, un sel, une huile, une encre, un cosmétique, un catalyseur, un détergent, un agent de traitement, un agent aromatique, un aliment, un combustible, un herbicide, un métal, une peinture, un agent photographique, un biocide, un pigment, un plastifiant, un carburant, un solvant, un agent stabilisant ou un additif polymère.
46. Procédé selon la revendication 1, dans lequel le matériau formateur de paroi est un poly(lactide), un poly(glycolide), un poly(caprolactone), un poly(hydroxybutyrate) ou des copolymères de ces produits.
47. Procédé selon la revendication 1, dans lequel le produit comprend un noyau central d'un agent entouré par une membrane extérieure.
48. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'agent est soluble dans le milieu d'élaboration continu, le milieu d'extraction ou les deux milieux.
49. Procédé selon la revendication 48, dans lequel l'agent est soluble dans l'eau, le milieu d'élaboration continu est un milieu aqueux et le milieu d'extraction est un milieu aqueux.